

The SPL Process ER/DL Sub-team meets on a bi-weekly basis.

Call-in Info is as follows:

Call Number: 1-412-777-7525

Conference ID: 427-139-451

Call Time: 1pm eastern

Here is the link to the Wiki page:

<http://spl-work-group.wikispaces.com/>

Meeting minutes are in red.

**SPL Process ER/DL Subteam Agenda 07-Mar-18 with minutes**

1. Lonnie Smith will speak to us about:

- a. **Product Concept Indexing File**

The validation procedure regarding the validation of the active ingredient information in incoming product SPL files with human drug and biological application numbers was included in the October 13, 2017, version of the SPL Implementation Guide and Validation Procedures accessible via this web page hyperlink:

<https://www.fda.gov/downloads/ForIndustry/DataStandards/StructuredProductLabeling/UCM321876.pdf>.

3.1.7.28 If the application number is referenced in any Product Concept Indexing file, then the active ingredient, strength and active moiety match a Product Concept Indexing file, except if the document type is *Lot Distribution Data* (66105-8) or *Indexing – Product Concept* (73815-3).

During a July 2015 Industry Upscale Working Group Process Team meeting the Product Concept Index file was discussed. SPL document authors responsible for the creation of files refer to the indexing files available for download from the National Library of Medicine (NLM). The same data is available in spreadsheet from the FDA webpage. During the initial phases of implementation one response from industry was about dosage form data. The dosage form data in the indexing files was often not aligned with the dosage form of the related SPL product file. For example, the data in the indexing file might have a dosage form “TABLET, EXTENDED RELEASE,” while the dosage form in the SPL file would be more specific, for example “TABLET, FILM COATED, EXTENDED RELEASE.” Due to the difficulty that would be involved in updating the thousands of SPL files, it was decided by FDA that dosage form would not be validated (SPL file validated against Product Indexing File) at that time.

During the same time period the Final Rule for Registration and Listing was published. As a result, the Product Concept Indexing file validation implementation was postponed. The text for the validation has been present in the implementation guide but the actual validation has not been

activated. FDA is planning to activate that validation procedure so that incoming files with an application number for an approved prescription drugs for human use are validated using the active ingredient information in the Product Concept Indexing File which has the same NDA or ANDA number.

One reason for the implementation of the Product Concept Indexing file validation is to ensure that the active ingredient information is as accurate as possible. In May of 2012, validation became active for the Active Ingredient, Active Moiety, and Basis of Strength information for human prescription drugs, human OTC drugs, animal drugs, etc. In that validation, UNII's and the term for the active ingredient, active moiety and basis strength are checked accuracy. In assessing the data received, there were issues related to the strength and dosage form. The solution to these issues was the development of the Product Concept Indexing file and its subsequent validation procedures.

Another reason for the current Product Concept Indexing file validation implementation relates to future indexing initiatives at FDA. Many of the errors in submitted SPL files at that time went beyond active ingredient, active moiety, and basis of strength. The implementation of the Product Concept Indexing file would serve to catch some of these errors.

Between 2012 and today the active ingredient information was validated based on the latest (most current) version of the SPL. Repackagers and Relabelers submit SPL files using the appropriate application numbers for the product. The SPL submitted by Repackers and Relabelers references the information in the original manufacturer's SPL file. FDA has been validating to ensure the information submitted with a particular application number is accurate based on the previous submission. However, if the original manufacturer submits their SPL, the system may check the repackager's and relabeler's SPL which may or may not have the information in the original manufacturers file. The resulting errors were sometimes inaccurate, but that error could be based on the original manufacturer's file OR the repackager's/relabeler's file. In order to reduce the number of manual overrides, Product Concept Indexing file validation will be activated. This will allow for incoming files to be validated against the Product Concept Indexing file instead of the previous version of the file with that application number.

SPL information is made available to DailyMed to be used in the ePrescribing System to generate the codes for electronic prescribing. When this information is not accurate it causes difficulty in the ePrescribing System. The information is also used downstream in clinical applications, the port (import/export) system, and OpenFDA. OpenFDA is maintained by FDA and this information is used in approximately 20,000 other applications worldwide. Other entities use SPL information to create mobile apps. If the information is not correct it also impacts anyone who is using that data downstream. The overall goal of the Product Concept Indexing file validation is to ensure data accuracy and data availability to downstream users in a timely manner.

The Product Concept Indexing file should alleviate the need for many manual overrides of the information submitted in an incoming file. Even if the information was incorrect in the previous version of the file, the system will generate another validation procedure based on the fact that the active ingredient information is different. The system will check the Product Concept Indexing file and if the data is correct then no manual override will be needed related to the active ingredient, active moiety, and basis of strength information.

A Product Concept Indexing file has not been created for every product at this time. If a Product Concept Indexing file has not yet been created, then the active ingredient, active moiety, basis of strength file will be used to validate the incoming file. If the active ingredient is not included in the active ingredient, active moiety, basis of strength file, then no validation of the active ingredient occurs. In the near future, validation against the Product Concept Indexing file will be the first validation that occurs on the active ingredient information in an SPL.

**Question:**

If the strength of an active is displayed on the label (in the content of labeling) as 100mg/4mL(25mg/1mL), will it make a difference which expression is used in the SPL file? Should we be referring to the Product Concept Indexing files to determine how the strength should be expressed in the SPL?

**Answer:**

Many of the Product Concept Indexing files use the normalized strength which will allow for the equivalent strength expression to be acceptable. This feature of the system has not been thoroughly tested at this time. The most current versions of the Product Concept Indexing files are updated through February 27, 2018 and they are available on DailyMed. The files will be updated frequently. These files can be automatically imported by software vendors just like any other indexing file.

**Question:**

When the Product Concept Indexing files are downloaded, there are a lot of files with various naming conventions, how can I quickly identify the file I need to use?

**Answer:**

FDA has created an excel spreadsheet which is posted on the SPL resources page with the other validation files.

**Question:**

If we proactively use the Product Concept Indexing spreadsheet to assess the information in our current drug listing and find that the information is not aligned, we will want to resubmit with the correct information. Will the resubmission of this SPL fail validation?

**Answer:**

Yes. You will need to simply request a manual override to upload the updated information to the FDA system. If you believe the information in the Product Concept Indexing files is not accurate, you can report that and request a review.

The Product Concept Indexing files can be found here (updated 3/7/2018):

<https://www.fda.gov/downloads/ForIndustry/DataStandards/StructuredProductLabeling/UCM498534.zip>

**Additional Comment:**

A new dosage form has been published: "TABLET WITH SENSOR." The dosage form will be available via the National Cancer Institute/Enterprise Vocabulary Services when the next update to that system occurs.

Lonnie sent me the below email to pass along:

Greetings,

As discussed during today's, March 7, 2018, industry SPL WG meeting, the updated Product Concept Indexing SPL file (data extraction) is now posted: <https://www.fda.gov/downloads/ForIndustry/DataStandards/StructuredProductLabeling/UCM498534.zip>.

Alternatively, as also discussed, the individual Product Concept Indexing SPL files can be accessed via DailyMed downloadable file: <https://dailymed.nlm.nih.gov/dailymed/spl-resources-all-indexing-files.cfm>.

Thank you,

Lonnie Smith

**2. Reminder:**

WIKI SURVEY- Please participate

The SPL Working Group WIKI has received the notice that the underlying site (wikispaces.com) will be closing its doors this year. I've looked at the usage statistics for the site, and we are still getting steady numbers of visitors and page access. Therefore, it's time to look for a new home for the WIKI. This gives all of us the opportunity to look at the site and provide input into how the new site can provide a better user experience. To do this, a brief (7 question at most) survey is now available from our WIKI homepage

(<http://spl-work-group.wikispaces.com> ) and directly through this link: <https://www.research.net/r/FGHTC67> . Please complete the survey as soon as you can, but definitely before **March 16**. If you are interested in being part of a small team who will design and build the new site (no coding should be required!), please reply to this e-mail.

3. Marcia Howard of Consumer Healthcare Products Association

a. Several years ago (2015), I received (by email) information from FDA that an export only product that follows manufacturing and labeling requirements could be issued a red ribbon certificate. If all monograph requirements aren't followed, a blue ribbon would be issued. We would like to see if companies are getting red or blue ribbon certificates for their OTC export only products and under what conditions if anyone is willing to share non-confidential information.

b. In addition, Sharon Rolfes of CBFleet provided the following additional information:

For several years up until about October 2016, we had been able to get export product CPPs with red ribbons (approved) by submitting CPP applications with both the US labeling and the export labeling as long we maintained drug listings for the export labeling, which we had. This demonstrated to the receiving country that the product formula was identical in both countries and only the labeling was different. This was an arrangement that CHPA had helped Fleet work out with the FDA. I do not know the details of the arrangement or how it came to be because it was before I took over filing applications.

In October, 2016 I received the first of several Returned for Action Notices from FDA for an export CPP because the application contained two sets of labeling. My colleague, Donna, had several conversations with FDA explaining the prior arrangement to no avail. However, even after this first rejection, some of the applications were approved with the dual labeling for at least a few months afterward. This is no longer the case, and at this point we have had no option but to apply for two CPPs for each product - one unapproved CPP for the export labeling which tends to cause problems with registrations, exportation, etc. AND one approved CPP for the US labeling.

We would just like to know 1) about the experience other companies have had with applying and receiving export product CPPs and 2) have they also had to file applications for two CPPs?

Herb found the below information on the topic which may be helpful to those who do have to deal with CPPs.

The FDA will issue a CPP for export only products. (CPP) Certificate of a Pharmaceutical Product are certificates that are requested by foreign customers or governments to supply a certificate related to articles subject to the Federal Food, Drug, and Cosmetic Act (FD&C Act), here is a link to the FDA page on CPPs:

<https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/ImportsandExportsCompliance/ucm348825.htm>

CPPs issued for drugs exported from the U.S. are printed on security paper and contain the signature of the authorized CDER Official, embossed federal seal, and ribbon. Different ribbon colors are used to designate the type of CPP issued, as follows:

- **Red** designates FDA-approved products, over-the-counter (OTC) products that follow an FDA monograph [[Example](#) (PDF - 2.34 MB)]
- **Blue** designates unapproved products [[Example](#) (PDF - 862 KB)]
- **Yellow** designates drugs manufactured in foreign facilities [[Example](#) (PDF - 1.88 MB)]
- **Orange** designates Active Pharmaceutical Ingredients (APIs) [[Example](#) (PDF - 1.79 MB)]

An Example from exports of Consumer Health products where CPP Certificates (Red) have been requested are:

- Guatemala because Myerstown ships 81mg there specifically for their market.

There are fees associated with the application not to exceed \$175.00 and will be issued within 20 days of application receipt.

- First certificate for the same country in the same application ..... \$175.00
- Second certificate for the same country in the same application ..... 90.00
- Third and subsequent certificates for the same country in the same application ..... 40.00

Payment is not expected at time of application but will be invoiced quarterly.

Herb will ask for a follow-up on this topic from his colleague (Julie) and this topic will be discussed at the next process team meeting. Ben will also reach out to his colleague at GSK to see if any additional information can be added.

4. Elias Macalalad at Jubilant:

- a. Last year, we created/submitted drug listings for products that we contract manufacture using marketing category "Approved Drug Product Manufactured Under Contract". This should have ensured that these CMO listings remain private. However, some of these drug listings ended up (and still remain) on DailyMed. In our correspondence with NLM, they indicated that we would need to submit updated files to the FDA with negative version numbers. Has anyone run into this problem? Is updating/submitting using negative version numbers the correct path?
- b. Many people have been finding this on DailyMed, myself included. Many have notified the FDA of this issue. I reached out to Lonnie Smith to see if there was a status update about this topic. Here is the response that he provided:
  - i. *A major system update is needed to programmatically remove the data due to the amount of files. In addition, the system update needs to be tested. Once FDA is satisfied with the update to the system then the SPL data will be removed from DailyMed.*
  - ii. *For the record, with the exception of the data in SPL files marked as "confidential," SPL files not posted on DailyMed can be requested by any*

*entity who submits to FDA a Freedom of Information Act request for the data not posted on DailyMed.*

**Update from Lonnie Smith:**

This system update will most likely occur during March of 2018. Another part of this issue is that sometimes companies are inadvertently submitting under a marketing category which posts to DailyMed. When they recognize this, they will then resubmit with a change marketing category "...manufactured under contract." Because DailyMed is external to FDA, the previous version remains on DailyMed until FDA manually creates a message requesting the listing be removed. Going forward, the FDA system will automatically send the removal request to DailyMed when this type of change occurs in a listing.

5. Debra Goetchius and Charlene Betz of Janssen:

- a. We would like to understand what others are doing:
  - i. Is it appropriate to only list the Distributor and not the manufacturer? Especially, when there may be more manufacturer of the drug product.
  - ii. Are there times when the manufacturer Name and Place of Business must be listed?
    1. Do State laws require this?
    2. What about third party manufacturers who do not fall under the Parent Company umbrella, are these manufacturers cited?
    3. What about off-shore (non-US) manufacturers that fall under the Company network but are unrelated to one another?

GSK has made a change in this language, now using "manufactured for..."

In the case of a third-party manufacturer, some companies are only listing on the packaging "manufactured for..." i.e. not including manufacturer name on the product packaging/label.

What about when there are multiple entities involved in the manufacturing of the product? Are companies listing all entities on the label?

Susan Crane mentioned that all PLD and third-party companies she has been involved with use either "manufactured for..." or "distributed by..."

Herb suggests that the guidance indicates that just including the distributor info will meet the requirements, but it maybe optional.

Link to the regulatory citation 21 CFR 201 (h):

<https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=201&showFR=1>

Some companies are also using "marketed by..."

**Question:**

Will the Pragmatic Validator tool validate against the Product Concept Indexing files?

**Answer:**

From Lonnie Smith: Once the validation procedure is implemented, yes.

**Question:**

What are the general uses of the Product Concept Indexing files?

**Answer:**

Typically, this file will be used by SPL authors who are not the innovator of a product. If you are not the innovator, your SPL information needs to match with the innovators SPL file information as indexed in the Product Concept Indexing files.